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Opioid-Induced Bowel Dysfunction

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Abstract

Opioid-induced bowel dysfunction (OIBD) is a potentially debilitating side effect of chronic opioid use. It refers to a collection of primarily gastrointestinal motility disorders induced by opioids, of which opioid-induced constipation (OIC) is the most common. Management of OIBD is difficult, and affected patients will often limit their opioid intake at the expense of experiencing more pain, to reduce the negative impact of OIBD on their quality of life. Effective pharmacologic therapy for OIC is considered an unmet need and several agents have recently been given priority review and approval for OIC. Furthermore, multiple agents currently in development show promise in treating OIC without significant impact on analgesia or precipitation of withdrawal symptoms. The approval and availability of such medications would represent a significant improvement in the management of OIC and OIBD in patients with chronic pain.

Keywords

Constipation; opioid; bowel dysfunction

INTRODUCTION

Chronic use of opioids to manage pain is common in clinical practice [1–3]. In the United States, opioid use has increased sharply over the past decade and it is estimated that approximately 3 % of the population receives long-term opioid therapy for chronic non-cancer pain [4]. Among patients who require chronic opioids, the balance between the incidence and severity of side effects and analgesia plays an important role in the success or

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Conflict of Interest

Gyanprakash A. Ketwaroo, Vivian Cheng, and Anthony Lembo declare that they have no conflict of interest

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failure of adequate pain management programs. The gastrointestinal (GI) tract is a particularly important source of opioid-related side effects, collectively termed opioid-induced bowel dysfunction (OIBD). Although opioid-induced constipation (OIC) is the most common side effect of opioids, other symptoms related to OIBD include nausea, vomiting, and dyspepsia [5]. Patients taking opioids may also suffer from decreased gastric emptying (often leading to gastroesophageal reflux and heartburn), abdominal cramping, spasm, and bloating [6–9]. Consequently, OIBD can have a dramatic negative impact on quality of life, both as a result of the direct, unwanted effects of opioids as well as a result of side effect-induced limitations of adequate dosing of narcotic analgesics.

FREQUENCY AND IMPACT OF OPIOID-INDUCED CONSTIPATION

In a survey of patients with non-cancer pain taking a median daily dose of 127.5 mg morphine-equivalent (range 7.5–600 mg) the most commonly reported GI side effect was constipation (46.9 %; 95 % CI 36.8–57.3), followed by gastro-esophageal reflux disease (33 %; 95 % CI 23.5–42.9), nausea (27 %; 95 % CI 17.2–35.3), and vomiting (9 %; 95 % CI 17.2–35.3) [10]. Chronic abdominal pain was also common (58.2 %; 95 % CI 53.2–73.9) and was associated with reduction in quality of life. A Cochrane systematic review of adults on opioids for non-cancer pain for at least 6 months found 22.0 % (95 % CI, 15.2–32.8) of patients discontinuing therapy due to adverse effects [11].

A multi-national study involving 322 patients taking oral opioids and laxatives found that OIC was most often characterized as severe, with 45 % reporting <3 bowel movements per week [12]. Importantly, nearly a third of patients altered their doses of opioid therapy in an attempt to mitigate the constipating side effects of these medications.

PATHOPHYSIOLOGY OF OPIOID-INDUCED GASTROINTESTINAL EFFECTS

The activity of opioids in the gut is mediated by μ-, δ-, and κ-opioid receptors, the distribution of which varies within the layers of the GI tract. In particular, μ-opioid receptors —through which most opioid analgesics function [13]—are present on the myenteric and submucosal neurons and on immune cells in the lamina propria. These receptors are present in the highest concentrations in the stomach and proximal colon [6, 14]. Endogenous opioids, such as met-enkephalin, leu-enkephalin, β-endorphin, and dynorphin [15], inhibit both propulsive motor and secretory activities [6].

Exogenous opioids cause constipation through multiple mechanisms. Through their effects on enteric neurons, opioids delay intestinal transit by stimulating nonpropulsive motility, increasing intestinal tone, and stimulating the pyloric and ileocecal sphincters [16]. Opioid agonists also stimulate fluid absorption in the gut by increasing contact time for absorption and stimulating mucosal sensory receptors. These agents also appear to inhibit chloride secretion by suppressing the excitation of cholinergic secretomotor neurons in the enteric nervous system [16]. Genetic polymorphisms and diversity may play a role in variation of people’s responses to opioids [17]. Such genetic diversity may impact the potential for developing OIBD, though the evidence for this remains limited.

MANAGEMENT OPTIONS FOR OPIOID-INDUCED CONSTIPATION

Since the dose that produces constipation is generally only 25 % of that required to provide adequate analgesia, simple opioid dose reduction is generally not an effective option for the management of OIC. Thus, alternative options for managing this condition must be explored.

Opioid rotation

Opioids have slightly different propensities to cause constipation in individual patients. Switching opioids, or “opioid rotation”, may be used as a strategy to relieve OIC or other adverse effects. A prospective trial enrolled 118 cancer patients at a single institution [18], who underwent opioid switching due to an unacceptable balance between analgesia and opioid-induced adverse effects. Eighty-one percent of substitutions were successful in finding a more acceptable balance between analgesia and adverse effects after the first switch in opioids and an additional 6 % responded after a second switch in therapy. The mean time required to identify an appropriate dose after switching was 3.2 days and the time to hospital discharge was directly related to the time needed to achieve dose stabilization. While this small trial suggests that algorithm-guided opioid rotation can be effective, prospective randomized trials regarding the efficacy and cost of this strategy are lacking and caution is necessary as equianalgesic doses can vary from person to person.

Novel opioids with less constipation

Few studies have directly compared the prevalence of GI side effects among opioids. Four controlled studies, however, found that transdermal fentanyl was associated with less frequent laxative use compared with morphine [19–22]. Tapentadol is a novel μ-opioid agonist that also inhibits norepinephrine, which is believed to augment its analgesic activity [23]. In a trial conducted in patients with lower back pain, tapentadol extended release 100–250 mg twice daily and oxycodone HCl controlled release 20–50 mg twice daily were both effective in controlling pain; however, the GI side effect profile of tapentadol was substantially better than that of oxycodone [24]. Similar results were seen in trials conducted in patients with moderate-to-severe chronic joint and back pain [25–28].

Adjunctive pharmacologic treatment

Laxatives—Conventionally, OIC is first approached through the use of laxatives such as osmotic (e.g., polyethylene glycol, magnesium) and stimulant laxatives (e.g., senna, bisacodyl). However, only about 50 % of patients experience satisfactory relief using this strategy [29, 30]. For this reason, treatment with laxatives often requires frequent dose adjustments, combination therapy, and laxative switching before achieving satisfactory results.

Lubiprostone—Lubiprostone, a chloride channel type 2 activator, is the only oral medication approved by the Food and Drug Administration (FDA) for use in chronic constipation and irritable bowel syndrome (IBS) with constipation. It was recently approved for treating OIC at a dose of 24 mcg twice daily, based on three Phase 3 randomized double-blind controlled trials involving patients with chronic non-cancer pain [31].

One Phase 3 trial, Study 1, was conducted in 431 patients with non-cancer-related pain treated with any opioid agonist except methadone. Subjects were randomized to lubiprostone 24 mcg twice daily or placebo for 12 weeks. This study's primary endpoint was the spontaneous bowel movement (SBM) response rate, defined as 3 or more SBMs per week for at least 9 weeks and at least 1 additional SBM per week over the mean at baseline. At the end of the 12-week treatment period, significantly more patients taking lubiprostone were "overall responders" compared with those receiving placebo (27.1 vs. 18.9 %, $p = 0.03$) [31].

In the other two identically designed Phase 3 trials, patients with chronic non-cancer pain on chronic opioid therapy including methadone received lubiprostone 24mcg twice daily or placebo for 12 weeks [31]. The primary endpoint was the mean change from baseline in the frequency of SBMs at week 8. In one study ($n = 418$), there was a statistically significant treatment difference of 0.9 SBM (3.3 vs. 2.4 for the lubiprostone and placebo treated groups, respectively; $p = 0.004$). Furthermore, there was a higher proportion of "overall responders" (3 or more SBMs per week for at least 9 weeks and at least 1 additional SBM per week over the mean at baseline),in the lubiprostone-treated group compared to the placebo group (24.3 vs. 15.3 %, respectively). In the third study ($n = 451$), there was no statistically significant change in SBM at week 8 for the lubiprostone treated group compared with placebo [31].

Among all three studies ($n = 1,492$), the most common adverse events in the lubiprostone group compared with the placebo group were nausea (11 vs. 5 %), diarrhea (8 vs. 2 %), and abdominal pain (4 vs. 1 %). There were no serious adverse events [31].

Naloxone—Naloxone, a competitive antagonist at opioid receptors with much higher affinity for μ-receptors than both κ- and δ-receptors, has been used to reverse OIC. Naloxone has a low oral systemic bioavailability due to extensive first pass-metabolism. Nevertheless, it is still widely distributed throughout the body and central nervous system, and when used at even a low dosage (2–4 mg three times daily) analgesia reversal and induction of opioid withdrawal symptoms can occur [32]. Combining oxycodone with naloxone has been shown to improve symptoms of constipation without significant reduction in analgesia for up to 52 weeks [33]. In a recent randomized control trial of 185 patients with chronic cancer pain, oxycodone/naloxone prolonged-release tablets were as effective as prolonged-release oxycodone in maintaining analgesia with significantly less constipation symptoms [34].

Methylnaltrexone—Methylnaltrexone, a quaternary ammonium derivative of naltrexone, is largely restricted to the periphery due to poor lipid solubility and is thus less likely than naloxone to reverse analgesia and induce opioid withdrawal symptoms [35]. It can be administered intravenously, subcutaneously, and orally, and all forms have been associated with a reduction in OIC. Only the subcutaneous administration form of methylnaltrexone is FDA approved for the treatment of OIC in advanced disease.

When administered intravenously, infusion of methylnaltrexone has been shown to reverse the constipation induced by methadone, increasing stool frequency and decreasing orocecal transit time [36, 37]. Subcutaneous methylnaltrexone was examined in 133 patients with

advanced illness and opioid-induced constipation that had not responded to ≥3 days of laxatives [38]. In the methylnaltrexone group, 48 % of patients had a bowel movement within 4 h after the first study dose compared to 15 % in the placebo group, and 52 % had a bowel movement within 4 h after ≥2 of the first four doses, compared with 8 % in the placebo group ($p \leq 0.001$ for both comparisons; Fig. 1). The response rate remained consistent throughout a 3-month extension trial. Evidence of withdrawal mediated by central nervous system opioid receptors or changes in pain scores was not observed. Abdominal pain and flatulence were the most common adverse events. Subsequent studies have confirmed a similar efficacy of subcutaneous methylnaltrexone at a dose of 12 mg either once daily or every other day in treating OIC [39–41]. Subcutaneous methylnaltrexone was approved by the FDA in 2008 for opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient [42]. It is usually dosed once every other day, but no more frequently than one dose in a 24-h period. The recommended dose of methylnaltrexone is 8 mg for patients weighing between 38 and 62 kg, 12 mg for patients weighing 62 to 114 kg, and 0.15 mg/kg for patients outside these ranges.

Results from a 12-week phase 3 trial in 803 patients with chronic non-cancer pain and OIC with oral methylnaltrexone (150, 300, or 450 mg; 4 weeks daily dosing, followed by 8 weeks PRN dosing) were recently presented [43]. Patients receiving the 300 and 450 mg doses achieved a statistically significant higher incidence of bowel movements without the need for laxatives compared with placebo. Throughout the study, there were minimal changes from baseline in pain intensity scores, regardless of the treatment group.

Alvimopan—Alvimopan is an oral μ-opioid receptor antagonist that does not cross the blood–brain barrier [44]. Alvimopan was approved by the FDA in 2008 for post-operative ileus with a Risk Evaluation and Mitigation Strategy due to an increased number of myocardial infarctions in one 12-month study. This imbalance has not been observed in other studies. While alvimopan is not approved for the management of OIC, it has been extensively studied for this indication. In one pivotal trial, 522 patients taking ≥30 mg of oral morphine and with associated constipation (i.e., <3 SBMs per week), were randomized to 6 weeks of alvimopan 0.5 mg twice daily, 1 mg once daily, 1 mg twice daily, or placebo. Alvimopan at all doses evaluated was associated with a significant increase in the mean number of SBMs per week over the first 3 weeks of treatment. Alvimopan was also associated with improvements in straining, stool consistency, incomplete evaluation, decreased appetite, and abdominal bloating/discomfort. In this study, the side effect profile of the 0.5 mg twice daily dose was similar to placebo [45].

Subsequently, two large Phase 3 clinical trials have been published comparing alvimopan 0.5 mg once daily, twice daily, or placebo for 12 weeks in non-cancer OIC [46, 47]. Only one of the two studies met the primary endpoint (i.e., the proportion of patients experiencing ≥3 SBM per week over the treatment period and an average increase from baseline of ≥1 SBM). Both studies showed improvement in straining, stool consistency, incomplete evacuation, and abdominal bloating/discomfort. Alvimopan did not significantly reverse opioid analgesia.

Agents under investigation

Naloxegol (formerly known as NKTR-118) is a combination of oral naloxol, a derivative of the opioid antagonist naloxone, and a polyethylene glycol moiety, which reduces first-pass metabolism, thereby increasing bioavailability and reducing penetration into the central nervous system. The results of two Phase 3 trials (KODIAC-04 and -05) and a safety extension trial for naloxegol were recently announced, although they have not yet appeared in a peer-reviewed literature [48]. Both studies evaluated the efficacy of 12 weeks of treatment with naloxegol 12.5 and 25 mg compared with placebo. The primary endpoint was response at 12 weeks defined as ≥3 SBMs per week with a ≥1 SBM increase over baseline for ≥9 of 12 weeks. In KODIAC-04, both the 12.5 and 25 mg doses of naloxegol demonstrated statistically significant results for the primary endpoint ($p = .015$ and 0.001, respectively). In KODIAC-05, only the 25-mg dose was statistically significant ($p = 0.021$). Arthralgia was the only adverse event that occurred at a greater frequency in the naloxegol 25-mg arm compared to placebo.

TD-1211 is an oral multivalent inhibitor of the μ-opioid receptor currently under investigation for the management of OIC. In a recent Phase 2 trial, 217 patients with non-cancer OIC were randomized to one of three doses of TD-1211 (5, 10, or 15 mg after a lead in period of 5 mg in all groups) or placebo for 5 weeks. All doses of TD-1211 met the primary endpoint of an increase in weekly average complete spontaneous bowel movements (CSBMs) over treatment weeks 2–5 compared to baseline. The placebo-treated group reported an increase from baseline of 0.8 CSBMs per week versus 2.5 ($p = 0.0003$), 2.6 ($p = 0.001$), and 1.5 ($p = 0.04$) CSBMs per week for the TD-1211-treated groups (15, 10, and 5 mg, respectively). The most common adverse events were abdominal pain, nausea, diarrhea, and headache and there was no adverse effect on analgesia with TD-1211 [49].

Benvenopran (CB-5945, formerly ADL5945) is another peripherally-acting μ-opioid receptor antagonist under investigation for OIC. Two Phase 2 trials recently compared benvenopran with placebo in patients with non-cancer chronic pain and OIC. The primary endpoint was change in SBMs over the 4-week treatment period. Benvenopran-treated patients receiving 0.25 mg daily and 0.25 mg twice daily showed statistically significant increases from baseline compared to those receiving placebo daily and twice daily (2.58, 3.42, 1.40, and 1.44 SBM, respectively). The most commonly reported adverse events were abdominal pain and upper respiratory tract infection. There were no changes in analgesic effect or evidence of CNS effects [50].

Prucalopride is a 5-HT_4 agonist that accelerates colonic transit in healthy humans and in patients with functional constipation. It is approved in the European Union and Canada for chronic idiopathic constipation. A Phase 2 trial randomized 196 chronic non-cancer pain patients with OIC and no history of chronic constipation prior to beginning opioid therapy to either prucalopide 2 or 4 mg or placebo for four weeks. The primary endpoint was the proportion of patients with an increase of at least ≥1 CSBM per week from baseline. During the first week of treatment, both prucalopride-treated groups had a statistically significant increase in the proportion of patients reporting an increase of ≥1 CSBM over the first week compared to placebo (43.8 % of prucalopride 2 mg, 50.0 % of prucalopride 4 mg, and 23.4 % of placebo-treated patients). When averaged over the 4 weeks, a greater proportion

of prucalopride-treated patients reported an increase of ≥1 CSBM per week from baseline (35.9 % with prucalopride 2 mg, 40.3 % with prucalopride 4 mg) compared to placebo (23.4 %); however, these differences did not reach statistical significance. The most common adverse events observed in these trials were abdominal pain and nausea [51].

S-297995 (Naldemedine) is an oral, peripherally acting μ-opioid receptor antagonist that recently completed a placebo-controlled single-ascending dose study in patients with OIC. Patients were randomized if they had chronic pain requiring 90 mg or more morphine equivalents daily for at least 3 months. A total of 75 subjects were randomized to one of six S-297995 cohorts: 0.01, 0.03, 0.1, 0.3, 1.0, or 3.0 mg. Preliminary results suggest that the medication was well tolerated with mild or moderate adverse events and no evidence of opioid central withdrawal and a dose-dependent increase from baseline in the number of SBMs [52].

Management Guidelines

The National Comprehensive Cancer Network (NCCN) and the American Academy of Pain Medicine (AAPM) have issued guidelines for the management of OIC [53, 54]. Both advocate prophylaxis including adequate fluid and fiber intake, laxatives, and stool softeners. While the AAPM suggest that there is insufficient evidence to recommend oral opioid antagonists to treat OIBD, the NCCN support the use of stool softeners, magnesium hydroxide, bisacodyl, lactulose, sorbitol, magnesium citrate, or polyethylene glycol, and/or the use of Fleets, saline, or tap water enemas. The NCCN also suggest opioid rotation to potentially less constipating agents, such as fentanyl or methadone, and the use of the opioid antagonist, methylnaltrexone, in severe cases.

CONCLUSION

Opioids are the foundation of the management of moderate to severe pain. Given the aging population and an increasing focus on improved management of pain, it is likely that chronic use of opioids, and OIBD, will continue to increase. For these reasons, it is critical for physicians to recognize the GI side effects of these agents and manage them appropriately. There is a broad range of management strategies for OIC with stimulant laxatives, with or without stool softeners, as the first-line pharmacologic treatment used in most patients. Unfortunately, these inexpensive and readily available agents rarely provide complete relief from OIC. In resistant patients, opioid rotation, lubiprostone, and methylnaltrexone should be considered. There have also been promising data on the benefits of investigational drugs such as benvenopran and naloxogel, among others. With current therapies and ongoing research into new pharmacological options, there is hope that eventually the impact of OIC and other GI side effects associated with chronic opioid use will be minimized while permitting adequate pain relief.

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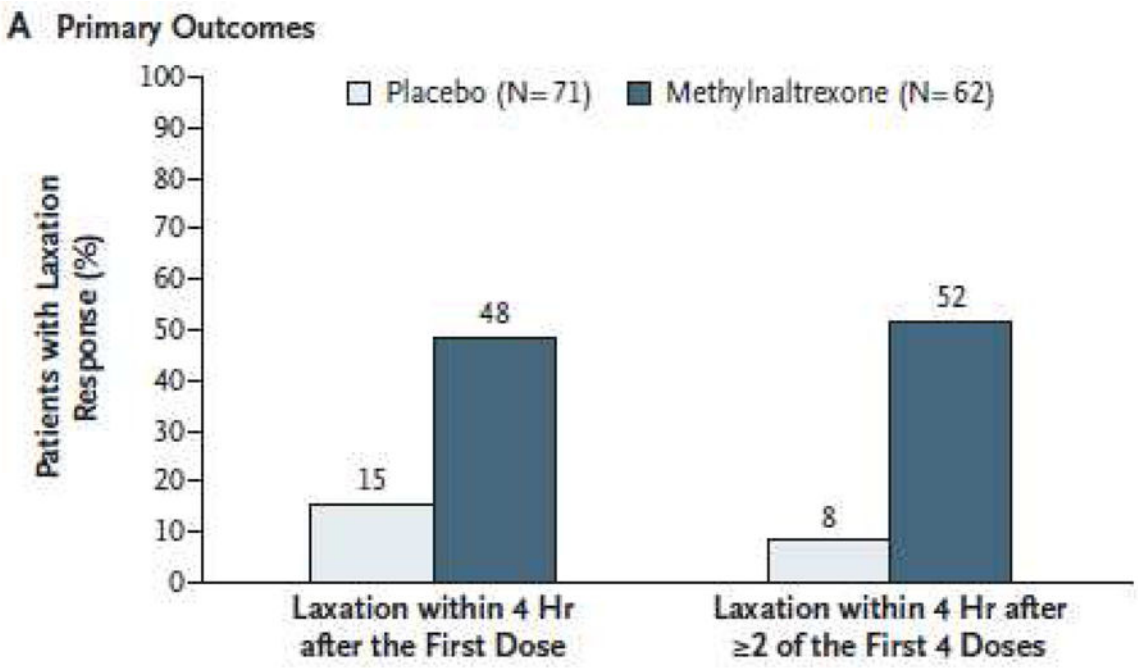

Figure 1.

Primary outcomes of a clinical trial comparing methylnaltrexone and placebo in patients with opioid-induced constipation [38]